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Chelation-Assisted C–H and C–C Bond Activation of Allylic Alcohols by a Rh(I) Catalyst under Microwave Irradiation

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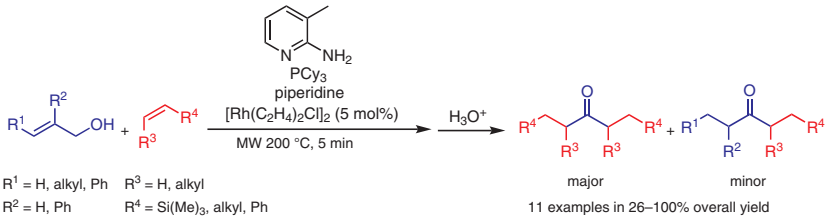

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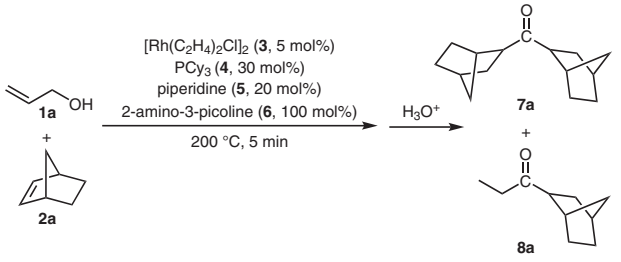
Abstract Chelation-assisted Rh(I)-catalyzed ketone synthesis from allylic alcohols and alkenes through C–H and C–C bond activations under microwave irradiation was developed. Aldimine is formed via olefin isomerization of allyl alcohol under Rh(I) catalysis and condensation with 2-amino-3-picoline, followed by continuous C–H and C–C bond activations to produce a dialkyl ketone. The addition of piperidine accelerates the reaction rate by promoting aldimine formation under microwave conditions.

Key words rhodium, transition metals, hydroacylation, C–C bond activation, chelation assistance, microwave irradiation

The activation of C–H and C–C bonds by transition-metal complexes is a current interest in organometallic chemistry.[1] In particular, hydroacylation of alkenes or alkynes with aldehydes is of great importance for the atom-economical production of the corresponding ketones.[2] We developed an efficient co-catalytic system for Rh(I)-catalyzed chelation-assisted hydroacylation using 2-amino-3-picoline as an organic catalyst.[3] While this catalytic system allowed aromatic aldehydes to react effectively with olefins to produce the corresponding ketones, aliphatic aldehydes undergo undesirable aldol condensation. Allyl alcohol has been used as an alternative substrate to aldehydes for hydroacylation to overcome this shortcoming because allyl alcohol can be converted into an aldehyde by olefin isomerization.[4] As soon as the aldehyde is formed, it is readily trapped by 2-amino-3-picoline to form aldimine, which is transformed into a ketone by chelation-assisted hydroacylation and hydrolysis. We also reported the C–C bond activation of ketones bearing β-hydrogen with the same protocol.[5] However, since the reaction-energy barrier for C–C bond activation of ketones is higher than that for C–H bond activation of aldehydes, more vigorous reaction conditions seem to be required. One of the best ways to achieve this goal is to carry out the reaction with microwave irradiation as a heating source.[6] Herein, we report the rhodium(I)-catalyzed synthesis of dialkyl ketones from allyl alcohols and alkenes under a modified co-catalyst system for chelation-assisted C–H and C–C bond activations under microwave irradiation. We also found that C–C bond activation with precedent C–H bond activation of aldehydes derived from allyl alcohol is more facile than the direct C–C bond activation of ketones.

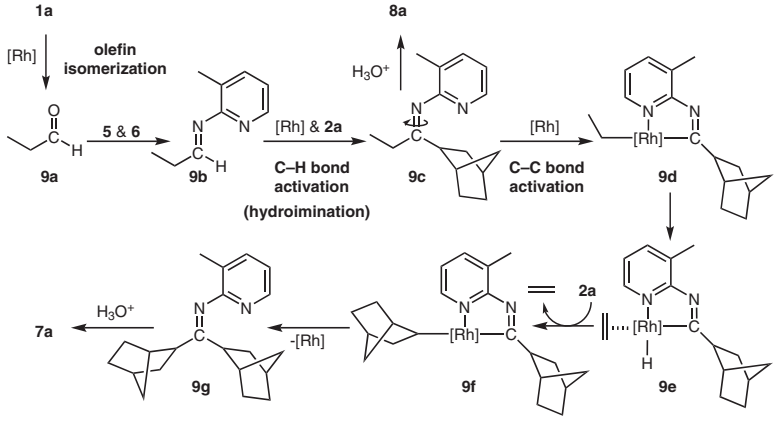
Table 1 Comparison of Different Heating Methods for the Rh(I)-Catalyzed Hydroacylation with Allyl Alcohol[a]



Entry	Activation mode	Time	Yield (%)[b]	
			7a	**8a**
1	MW	5 min	93	7
2	Δ	5 min	5	1
3	Δ	12 h	40	3

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (1.2 mmol), **3** (5 mol%), **4** (30 mol%), **5** (20 mol%), and **6** (100 mol%).
[b] Yield of **7a** and **8a** was determined by GC-MS analysis with mesitylene as an internal standard.

When the reaction of allyl alcohol (**1a**) with norbornene (**2a**) was carried out in the presence of $[Rh(C_2H_4)_2Cl]_2$(**3**) with tricyclohexylphosphine (**4**), piperidine (**5**), and 2-amino-3-picoline (**6**) at 200 °C for 5 min under MW irradiation



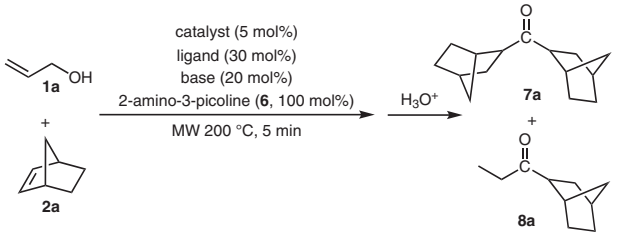
Scheme 1 A plausible mechanism for the Rh(I)-catalyzed hydroacylation with allyl alcohols and alkenes through C–H and C–C bond activation

conditions, dinorbornyl ketone **7a** was obtained in 93% yield along with a 7% yield of norbornyl 3-propanone (**8a**, Table 1, entry 1). It is thus believed that **8a** is an initial hydroacylation product while **7a** is the product of the subsequent C–C bond cleavage. MW irradiation is very efficient, since only a 5% yield of **7a** was obtained with conventional heating (Δ) under identical reaction conditions (Table 1, entry 2). Even with a long reaction time of 12 h, only a 40% yield of **7a** was obtained (Table 1, entry 3). The beneficial effects of microwave irradiation are likely due to the fact that the dipole–dipole electrostatic interactions of microwave irradiation accelerate the condensation reaction by stabilizing the polar transition state between 2-amino-3-picoline (or piperidine) and aldehydes generated by the isomerization of allyl alcohol.[6]

A plausible mechanism is depicted in Scheme 1. The reaction consists of three consecutive reactions; isomerization of allyl alcohol, chelation-assisted C–H bond activation, and C–C bond activation. Initially, allyl alcohol (**1a**) is isomerized to propanal (**9a**) by Rh(I). As soon as propanal is formed, it condenses with 2-amino-3-picoline (**6**) to generate aldimine **9b**, which is hydroiminated with an alkene to form **9c** through chelation-assisted C–H bond activation by Rh(I). Further chelation-assisted C–C bond activation of **9c** by Rh(I) affords **9d**, which undergoes β-elimination to form **9e** with the liberation of ethylene. Insertion of another alkene **2a** into Rh(I)–H and reductive elimination of the resulting **9f** gives ketimine **9g**. Finally, symmetric dialkyl ketone **7a** is produced by hydrolysis of **9g**.

Various catalytic conditions were investigated to optimize the reaction (Table 2). Alkyl phosphine showed better formation of the C–C bond-cleaved product **7a** than did aryl phosphine, since the reaction with Rh(I) catalyst **3** with PCy_3 or P(*n*-Bu)$_3$ gave much higher yields than that with PPh_3 (Table 2, entries 1–3). However, $Rh(PPh_3)_3Cl$ improved the yield of **7a** slightly, reaching 50% (Table 2, entry 4). Compared with phosphine ligands, N-heterocyclic carbene (NHC) ligands such as 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) or 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) did not give good results (Table 2, entries 5 and 6). On the other hand, the yields of C–H bond activation product **8a** were 41% and 54% for IMes and IPr, respectively. This fact suggests that the selectivity of **7a** and **8a** can be controlled by the type of ligand. Employing different catalysts, $[Rh(COE)_2Cl]_2$ or $[Rh(COD)Cl]_2$ with PCy_3 did not improve the yield of the C–C bond-cleaved product (Table 2, entries 7 and 8). Of the various amine additives, piperidine and diethylamine showed better results than those of primary amines like Cy-NH_2 (Table 2, entries 1 and 10–12). This behavior is suggested to occur because secondary amines accelerate the transimination more effectively than primary amines, as shown in Scheme 2. The transimination acceleration effect of secondary amines was studied by M. B. Cid in the condensation of aldehydes and amines to form imines.[7]

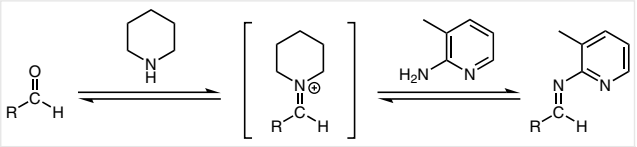
Table 2 Optimization of the Rh(I)-Catalyzed Hydroacylation with Allyl Alcohol through C–H and C–C Bond Activation[a]



Entry	Catalyst	Ligand	Base	Yield (%)[b]	
				7a	**8a**
1	$[Rh(C_2H_4)_2Cl]_2$ (**3**)	PCy_3 (**4**)	piperidine (**5**)	93	7
2	**3**	P(*n*-Bu)$_3$	**5**	80	14
3	**3**	PPh_3	**5**	35	61
4	$Rh(PPh_3)_3Cl$	–	**5**	50	50
5	**3**	IMes[c]	**5**	8	41

Entry	Catalyst	Ligand	Base	Yield (%)[b]	
				7a	8a
6	**3**	IPr[d]	**5**	4	54
7	$[Rh(COE)_2Cl]_2$	**4**	**5**	75	18
8	$[Rh(COD)Cl]_2$	**4**	**5**	31	30
9	**3**	**4**	–	71	9
10	**3**	**4**	diethyl amine	84	15
11	**3**	**4**	Cy-NH_2	75	13
12	**3**	**4**	aniline	67	10

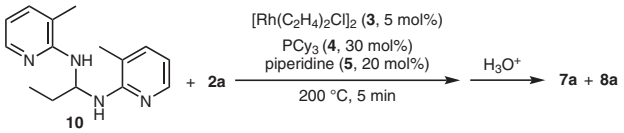
[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (1.2 mmol), catalyst (10 mol% [Rh]), ligand (30 mol%), base (20 mol%), and **6** (100 mol%).
[b] Yield of **7a** and **8a** was determined by GC-MS analysis with mesitylene as an internal standard.
[c] IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.
[d] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.



Scheme 2 Accelerating effect of piperidine in the formation of aldimine

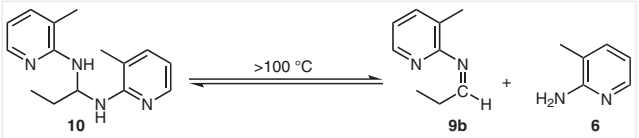
In this reaction, we suggest that the microwave heating affects the formation rate of aldimine rather than the rate of the C–H and C–C bond-activation steps, since the reaction rates of C–H and C–C bond activation of aldimine were almost identical under thermal and MW irradiation, as shown in Table 3. Aminal **10** was used as an imine precursor to aldimine **9b** because it dissociates to aldimine and 2-amino-3-picoline above 100 °C (Scheme 3).[8] When the reaction of norbornene **2a** and aminal **10** (prepared by condensation of propanal with 2-amino-3-picoline) was carried out at 200 °C for 5 min in the presence of the same catalysts under thermal and MW conditions, 91% and 81% yields of **7a** were obtained, respectively. This result suggests that formation rate of aldimine from allyl alcohol is crucial to the overall reaction rate.

Table 3 The Rh(I)-Catalyzed Hydroacylation with Aminal through C–H and C–C Bond Activation[a]



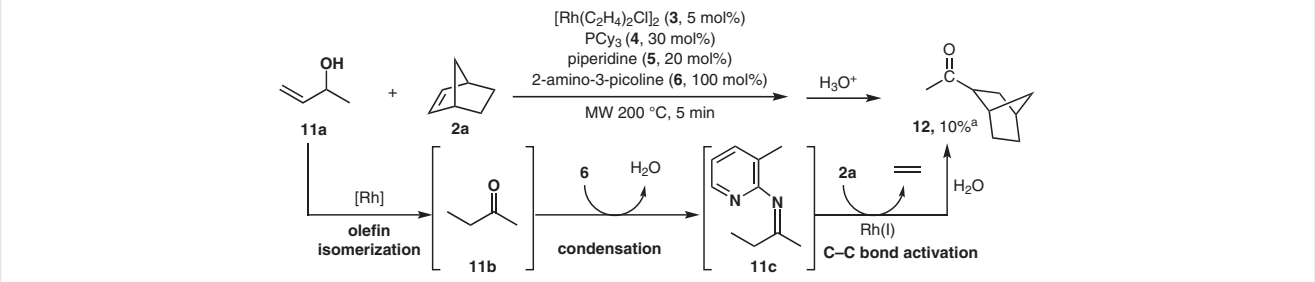
Entry	Activation mode	Ratio of **7a**/**8a**	Overall yield (%)[b]
1	MW	91: 9	100
2	Δ	84:16	96

[a] All reactions were carried out with **10** (0.2 mmol), **2a** (1.2 mmol), **3** (5 mol%), **4** (30 mol%), and **5** (20 mol%).
[b] Overall yield of **7a** and **8a** was determined by GC-MS analysis with mesitylene as an internal standard.



Scheme 3 Dissociation mechanism of aminal to aldimine and picoline

We also found that the reaction of 3-buten-2-ol (**11a**) with norbornene (**2a**) afforded only a 10% yield of the C–C bond-cleaved product **12** (Scheme 4); in contrast, the reaction of allyl alcohol gave a 93% yield of the C–C bond-cleaved product **7a** (see Scheme 1). Although the reaction of **1a** with alkenes requires more steps than that of **11a**, including C–H bond activation, the reaction is much more facile. This outcome can be explained as follows. It seems to be difficult to generate ketimine **11c** from 2-amino-3-picoline and ketone **11b** (formed by isomerization of **11a**). However, in the case of allyl alcohol, aldimine **9b** is readily formed from the generated aldehyde and 2-amino-3-picoline. The subsequent hydroimination of **9b** leads to the facile formation of ketimine **9c**, which is directly involved in C–C bond activation. It is known that condensation of aldehydes and amines is easier than that of ketones and amines.[9]

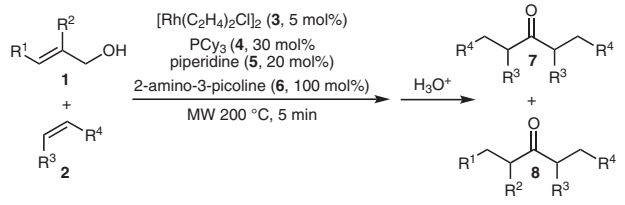


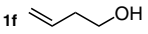
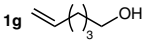
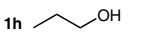
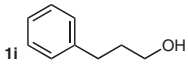
Scheme 4 The Rh(I)-catalyzed hydroacylation with 1-methylallyl alcohol through C–C bond activations and a plausible mechanism. *Reaction conditions*: **11a** (0.2 mmol), **2a** (1.2 mmol). [a] Yield of **12** was determined by GC-MS analysis with mesitylene as an internal standard.

Various substituted alkenyl alcohols were applied in this reaction (Table 4, entries 2–7). The reaction of allyl alcohols bearing 3-substituents like **1b**, **1c**, and **1d** (Table 4, entries 2–4) showed similar high reactivities (95–100% yields), while that of 2-substituted allyl alcohol **1e** (Table 4, entry 5) gave a low yield (65%) of product. The reaction of *n*-alkanal **13a** and *sec*-alkanal **13b** were compared to determine that the low yield of **1e** was due to the difference in olefin isomerization rate (Table 5, entries 1 and 2). With **13a**, 100% yield of **7a** and **8d** was obtained, while only a 53% yield of **7a**/**8e** was produced with **13b**. These results are very similar to those of **1d** and **1e**. Therefore this difference in yield of **1d** and **1e** is likely because the aldimine derived from **1e** is a sterically hindered *sec*-alkyl aldimine, which is difficult to carry out hydroimination.[3a]

The reactions of nonallylic alcohols like 3-butenol (**1f**), 5-hexenol (**1g**), 1-propanol (**1h**), and 3-phenylpropanol (**1i**) afforded very low yields (20–60%) of the corresponding C–H and C–C cleaved products. In these cases, the formation rate of the aldehyde might be very low due to difficult olefin isomerization of **1f** and **1g**, and more difficult transfer hydrogenation of **1h** and **1i** (Table 4, entries 6–9). The reaction was carried out with various olefins (Table 4, entries 10–15). The reactions of common terminal olefins were sluggish compared with that of norbornene (**2a**). Yields of the products were 65–83%. The reason must be that there is not much energy stabilizing effect by transforming terminal olefins into alkyl groups, while ring-strained norbornene (**2a**) is transformed into the strain-free acylnorbornyl group during C–H bond or C–C bond activation. With cyclohexene (**2g**), only 26% yield of corresponding products of **7g** and **8k** were obtained. Interestingly, vinylsilane **2b** was more reactive than *tert*-butyl ethylene **2e** (Table 4, entries 10 and 13).

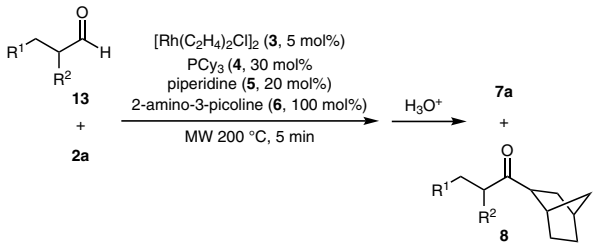
Table 4 Rh(I)-Catalyzed Hydroacylation with Various Alcohols and Alkenes through C–H and C–C Bond Activations[a]



Entry	**1** (R^1, R^2)	**2** (R^3, R^4)	Ratio of **7**/**8**	Overall yield (%)[b]
1	**1a** (H, H)	 **2a**	**7a**/**8a** (93:7)	100
2	**1b** (Me, H)	**2a**	**7a**/**8b** (89:11)	95
3	**1c** (*n*-Pr, H)	**2a**	**7a**/**8c** (88:12)	99
4	**1d** (Ph, H)	**2a**	**7a**/**8d** (88:12)	100
5	**1e** (H, Ph)	**2a**	**7a**/**8e** (69:31)	65
6	 **1f**	**2a**	**7a**/**8b** (91:9)	30
7	 **1g**	**2a**	**7a**/**8c** (100:0)	23
8[c]	 **1h**	**2a**	**7a**/**8a** (100:0)	20
9[c]	 **1i**	**2a**	**7a**/**8d** (78:22)	60
10[d]	**1a**	**2b** (H, $Si(Me)_3$)	**7b**/**8f** (51:49)	83
11[d]	**1a**	**2c** (H, Ph)	**7c**/**8g** (68:32)	69
12[d]	**1a**	**2d** (H, *n*-Bu)	**7d**/**8h** (77:23)	66
13[d]	**1a**	**2e** (H, *t*-Bu)	**7e**/**8i** (69:31)	65
14[d]	**1a**	**2f** (H, Cy[e])	**7f**/**8j** (71:29)	66
15[d]	**1a**	 **2g**	**7g**/**8k** (54:46)	26

[a] All reactions were carried out with **1** (0.2 mmol), **2a** (1.2 mmol), **3** (5 mol%), **4** (30 mol%), **5** (20 mol%), and **6** (100 mol%).
[b] Overall yield of **7** and **8** was determined by GC-MS analysis with mesitylene as an internal standard.
[c] 10 equiv of **2a** were used
[d] 10 equiv of **2a**, 10 mol% of **3** and 300 mol% of **6** were used.
[e] Cy = cyclohexyl

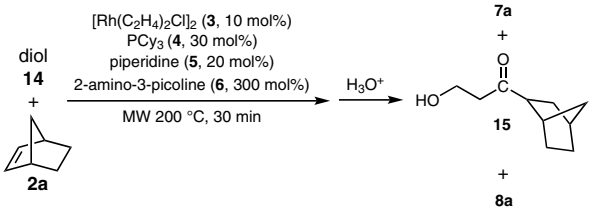
Table 5 The Rh(I)-Catalyzed Hydroacylation with Aldehyde through C–H and C–C Bond Activation[a]



Entry	**13** (R^1, R^2)	Ratio of **7a**/**8**	Overall yield (%)[b]
1	**13a** (Ph, H)	**7a**/**8d** (79:21)	100
2	**13b** (H, Ph)	**7a**/**8e** (60:40)	53

[a] All reactions were carried out with **13** (0.2 mmol), **2a** (1.2 mmol), **3** (5 mol%), **4** (30 mol%), **5** (20 mol%), and **6** (100 mol%).
[b] Overall yield of **7a** and **8** was determined by GC-MS analysis with mesitylene as an internal standard.

Table 6 Rh(I)-Catalyzed Hydroacylation with Diols through C–H and C–C Bond Activation[a]



Entry	Diol	Ratio of **7a**/**15**/**8a**	Overall yield (%)[b]
1	**14a** HO⁄⁄OH	88 / 7 / 5	100
2	**14b** HO⁄⁄⁄OH	75 / 20 / 5	51

[a] All reactions were carried out using **14** (0.2 mmol), **2a** (2.0 mmol), **3** (10 mol%), **4** (30 mol%), **5** (20 mol%), and **6** (300 mol%).
[b] Overall yield of **7a**, **15**, and **8a** was determined by GC-MS analysis with mesitylene as an internal standard.

The reaction of 2-butene-1,4-diol (**14a**) with norbornene (**2a**) produced a mixture of **7a**, **15**, and **8a** in an 88:7:5 ratio (Table 6). In this reaction, twice the amount (176% yield based on the number of moles of **14a**) of **7a** is produced. This effect is likely to occur because another allyl alcohol (**1a**) is generated during the reaction of **14a** with an alkene. Thus, **14a** should be regarded as two moles of allyl alcohol, which gives a theoretical yield of 88% of **7a**. This reaction mechanism is depicted in Scheme 5. Initially, **14a** is transformed into 4-hydroxybutanal (**16a**), which reacts with an alkene to form ketimine **16b**. Hydrolysis of **16b** gives **15**. Further C–C bond activation and β-hydrogen elimination of **16b** generates ketimine **9g** and allyl alcohol **1a**, which also participates in a further C–H and C–C bond activation to give another ketimine **9g**. Finally, **7a** is obtained by hydrolysis of **9g** produced from two different routes.

Butane-1,4-diol (**14b**) also reacts with alkenes to produce the same products in an overall yield of 51%, which is less than that of the reaction of **14a**. The reaction mechanism is almost identical except for the formation of 4-hydroxybutanal (**16a**). In this case, **16a** is generated by the transfer hydrogenation of the alcohol group in **14b**, which requires more harsh conditions than the olefin isomerization of **14a**. In this case, the rate-determining step may be dehydrogenation of alcohol to form **16a**, which slows down the overall reaction rate.

In conclusion, the reaction of allyl alcohol with an alkene in the presence of a Rh(I) catalyst allows the formation of ketone through olefin isomerization of allyl alcohol, followed by chelation-assisted C–H bond and C–C bond activation.[10,11] In this reaction, allyl alcohol is used as a carbonyl source for symmetric dialkyl ketone compounds.

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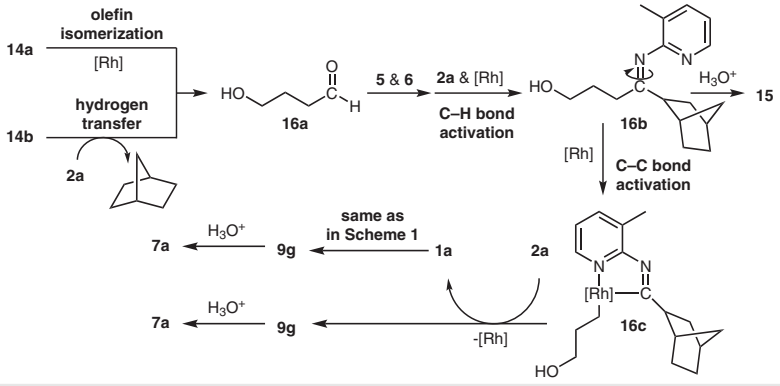

Scheme 5 Plausible mechanism for Rh(I)-catalyzed hydroacylation with diols through C–H and C–C bond activations

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(10) **Typical Procedure for the Rh(I)-Catalyzed Hydroacylation with Allyl Alcohol through C–H and C–C Bond Activation**
To a 10 mL thick-walled Pyrex tube were added allyl alcohol (**1a**, 13.6 µL, 0.2 mmol), norbornene (**2a**, 113.0 mg, 1.2 mmol), $[Rh(C_2H_4)_2Cl]_2$(**3**, 3.9 mg, 0.01 mmol), 2-amino-3-picoline (**6**, 20.2 µL, 0.2 mmol), and tricyclohexylphosphine (**4**, 16.8 mg, 0.06 mmol), and piperidine (**5**, 4.0 µL, 0.04 mmol). The reaction vessel was capped with a Teflon septum and installed in a CEM Discover microwave reactor. The reaction was carried out with internal magnetic stirring at 200 °C under microwave irradiation. After cooling, the reaction mixture was filtered through a short column filled with silica and washed with CH_2Cl_2 and ethyl acetate. The filtrate was analyzed by GC-MS and determined to be 93% of dinorbornyl ketone (**7a**) and 7% of norbornyl 3-propanone (**8a**).

(11) **Synthesis of *N,N′*-Bis(3-methylpyridin-2-yl)propane-1,1-diamine (10)**
Propionaldehyde (**9a**, 500 mg, 8.60 mmol) was added to 2-amino-3-picoline (**6**, 1.73 mL, 17.2 mmol) and 4 Å MS at room temperature. When the mixture was stirred at room temperature for 12 h, a pale yellow solid formed. It was dissolved in methylene chloride and filtered. The resulting solution was concentrated and then re-crystallized from a methylene chloride/hexane mixture, then filtered and dried in vacuo to give the aminal **10** as white solid (1.79 g, 81%). ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.97 (d, *J* = 4.0 Hz, 2 H), 7.16 (d, *J* = 6.8 Hz, 2 H), 6.49 (dd, *J* = 5.2, 7.2 Hz, 2 H), 5.73 (d, *J* = 5.73 Hz, 2 H, NH), 5.57–5.53 (m, 1 H), 2.28–2.25 (m, 2 H), 2.02 (s, 6 H), 1.01 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 145.1, 137.2, 117.9, 113.1, 63.8, 27.6, 17.4, 11.4 ppm. IR (CH_2Cl_2): 3415, 3379, 2966, 2947, 2875, 1598, 1581, 1506, 1487, 1463, 1413, 1334, 1325, 1282, 1188, 1149, 1114, 1031, 779 cm^{-1}. Aminal **10** is determined as aldimine **9b** in HRMS. ESI-HRMS: *m/z* calcd for $C_9H_{12}N_2$148.1000; found: 149.1050 [M + H$^+$].